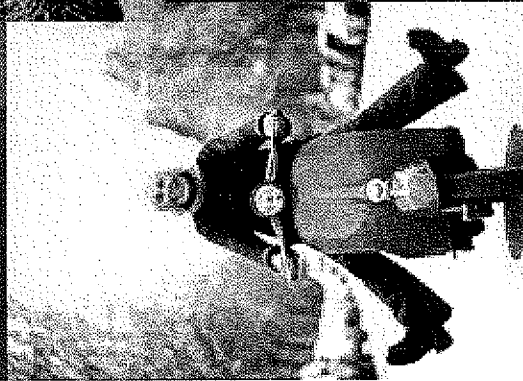


FemmePharma Global Healthcare, Inc.



***Delivering the Difference
in Women's Healthcare***



FemmePharma
GLOBAL HEALTHCARE, INC.

Transdermal vs Mammary vs Topical Delivery

- **Transdermal Delivery**
 - **Through the skin with the intent of systemic delivery**
 - **Bypass intestinal and hepatic metabolism**
 - **Usually applied at site remote to target organ**



FemmePharma
CLONAL PHARMACEUTICALS, INC.

Transdermal vs Mammary vs Topical Delivery

- **Mammary Delivery**
 - **Through the skin with the intent of regional delivery to underlying breast tissue**
 - **Analogous to pulmonary or intranasal administration**
 - **Achieve high regional concentrations for binding at receptors in the breast**
 - **Minimal systemic exposure**



FemmePharma
FLORENCE, ILLINOIS

Transdermal vs Mammary vs Topical Delivery

- **Topical Dermal Delivery**
 - **Direct application to the skin with the intent of working within the skin itself**
 - **Minimal systemic or regional involvement.**

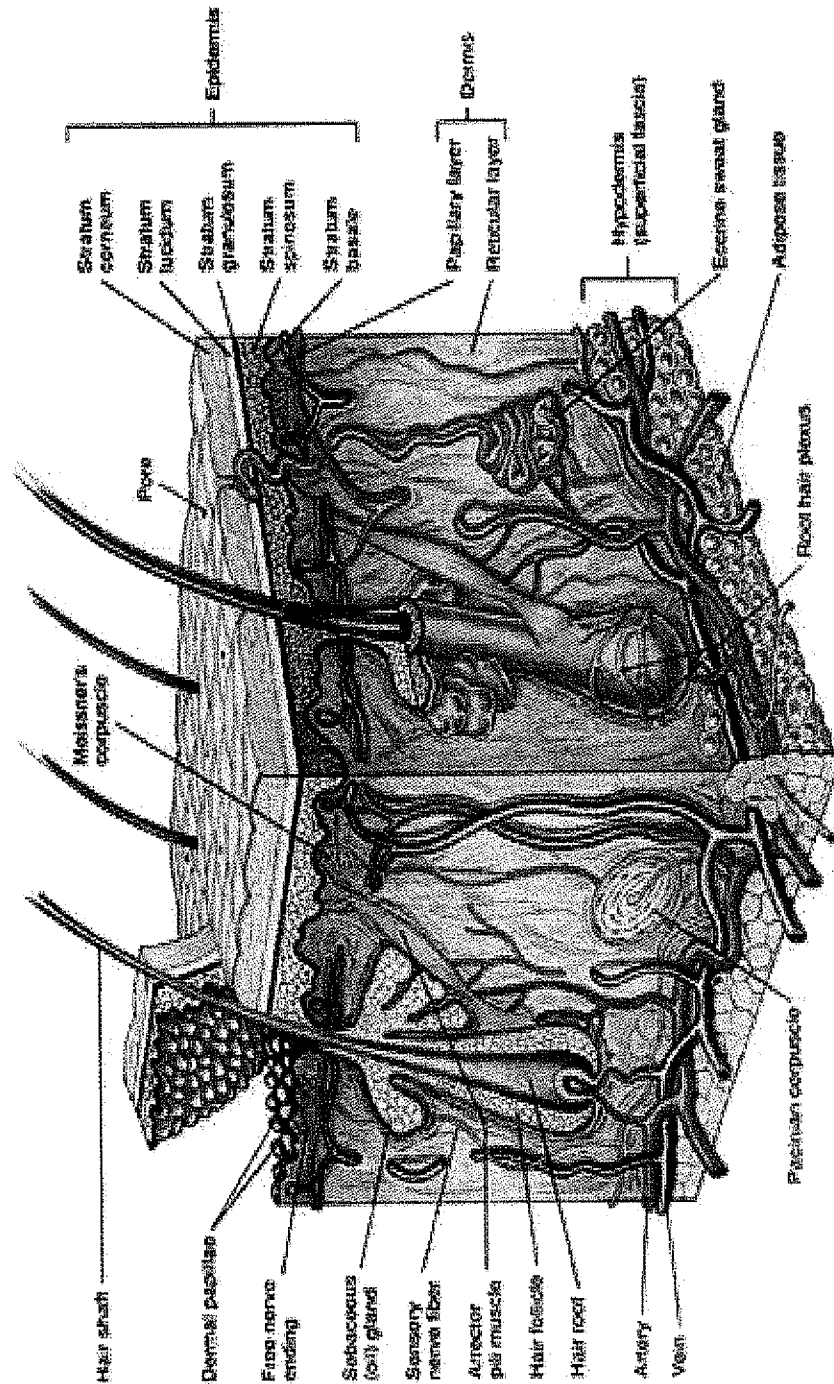


FemmelPharma
GLENDALE, CALIFORNIA, USA

Anatomy of Normal Skin

FIGURE 3

Structure of the Skin Membrane



RemmePharma
COSMETIC HEALTHCARE, INC.

Vaginal Epithelium

Figure 2

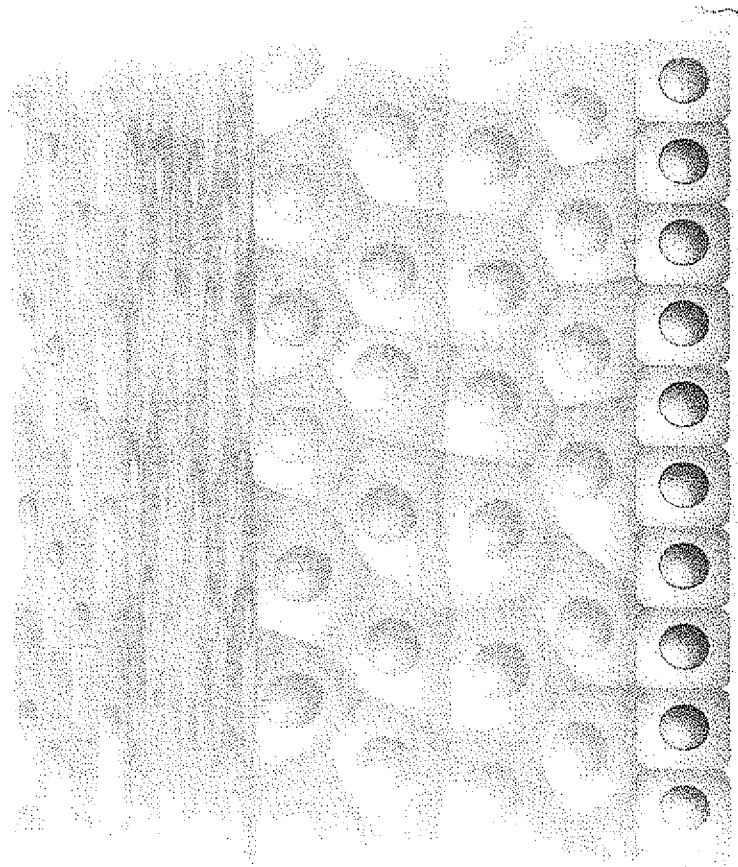
The Vaginal Epithelium

Superficial cells

Intermediate cells

Parabasal cells

Basal cells



FemmelPharma
GYNAL RESEARCH, INC.

Epithelial Cell

Apical plasma membrane

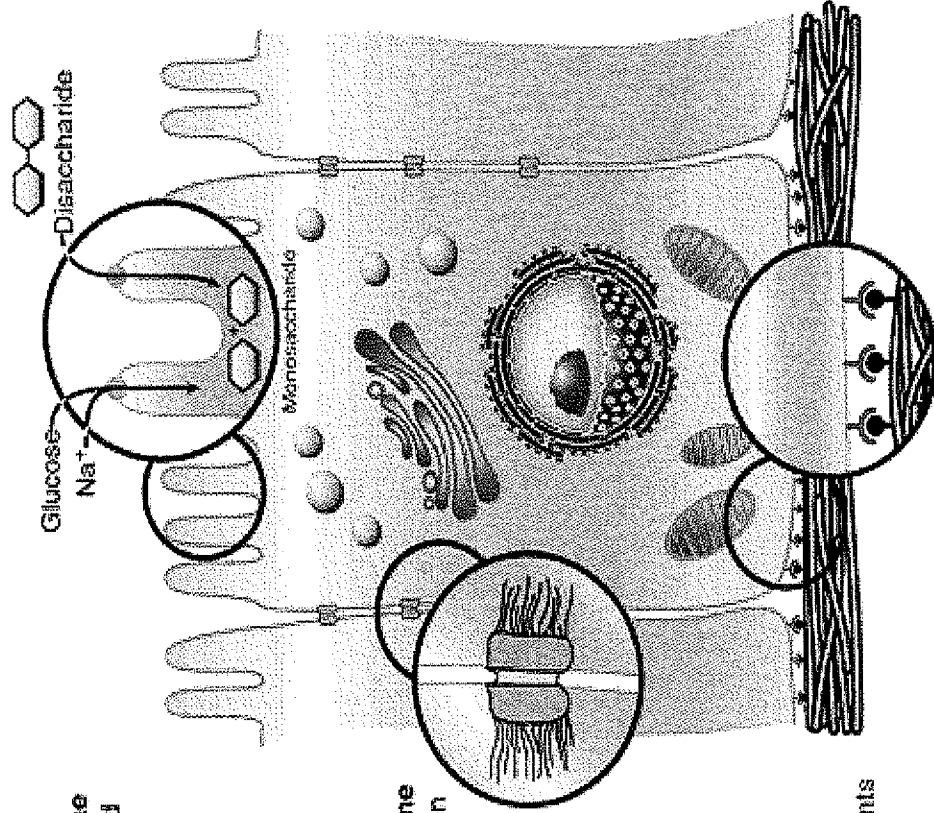
- regulation of nutrient and water intake
- regulated secretion
- protection

Lateral plasma membrane

- cell contact and adhesion
- cell communication

Basal membrane

- cell-substratum contact
- generation of ion gradients



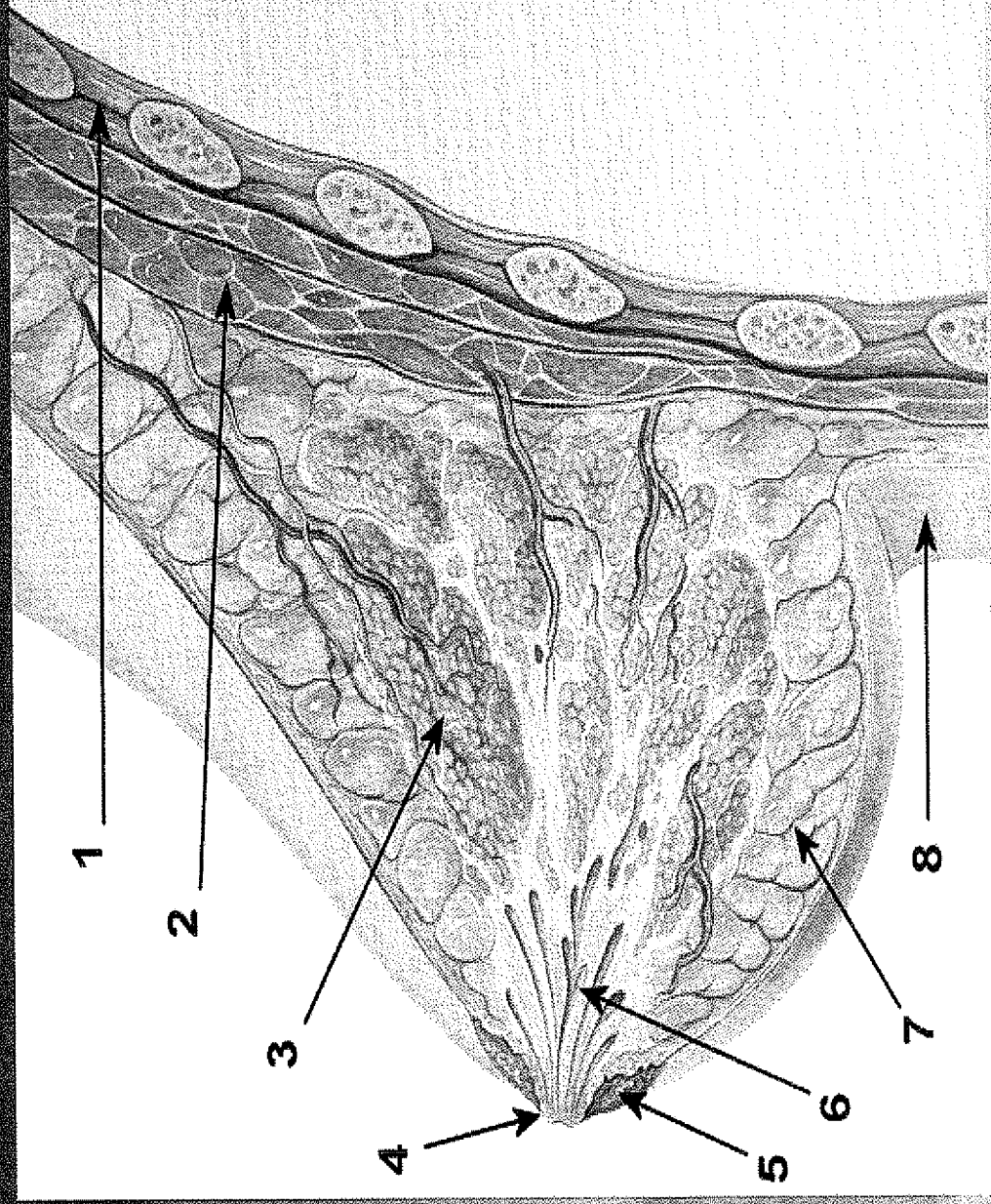
(a)

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FemmelPharma
CELLULAR RESEARCH, INC.

Anatomy of the Female Breast



FemmePharma
A Division of Allergan, Inc.

Formulation Comparisons

• Application Site	Breast	Vagina
• Indication	Breast Pain	Endometriosis
• Appearance	Colorless-yellow tinge, <i>clear</i> , semi-lucent	White, <i>opaque</i>
• Properties	Gel with <i>solubilized</i> danazol	Gel with danazol in <i>suspension</i>
• Particle Size	Solution	Micro/nanoparticles
• Excipients	Enhancer/Solubilizing	None
• Danazol		
Concentration	2% (w/w)	47% (w/w)
• Volume	>1ml/breast	200ul



FemmePharma
GLOBAL PHARMACEUTICALS, LLC

Reviewer's Comments

WO Application

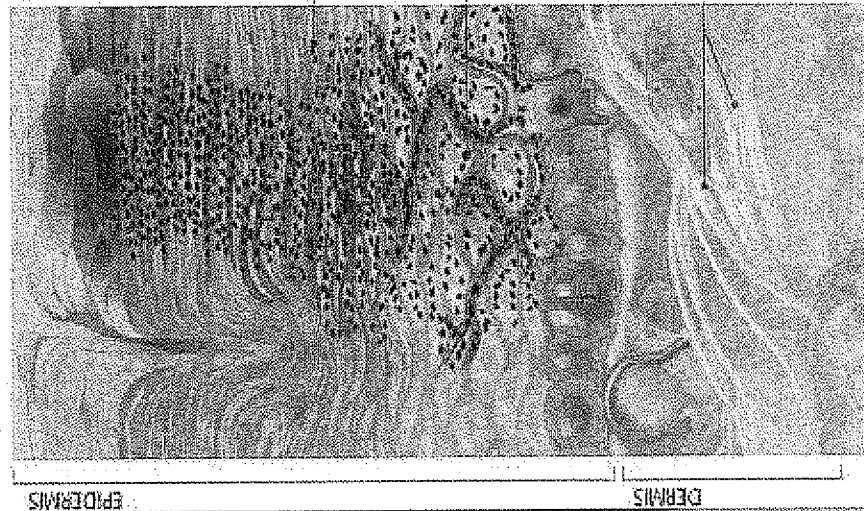
- Transdermal for systemic drug administration
- FP contemplates high breast levels with minimal systemic concentrations
- We removed micro and nanoparticles
- Double patenting(5,993,856)-marked differences in formulations gel vs suspension



FemmePharma
CLONING, REGENERATION, LIFE

Sun Induced Damage to Skin

DAMAGED SKIN



EPIDERMIS

DERMIS

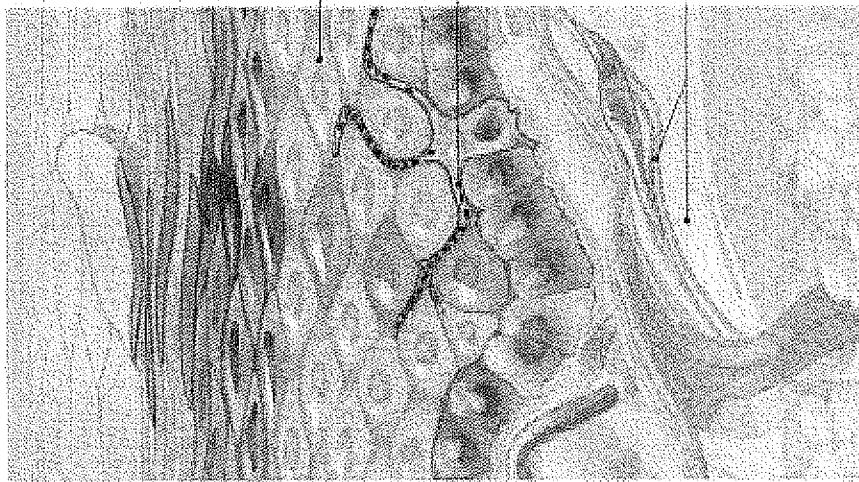
stratum corneum is thick and dehydrated

skin cells are misshapen and disorganized

excess melanin causes freckles and age spots

collagen and elastin fibers are weak and damaged

HEALTHY SKIN



EPIDERMIS

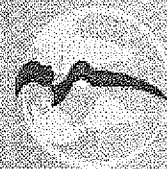
DERMIS

stratum corneum is thin and hydrated

new skin cells are healthy and full

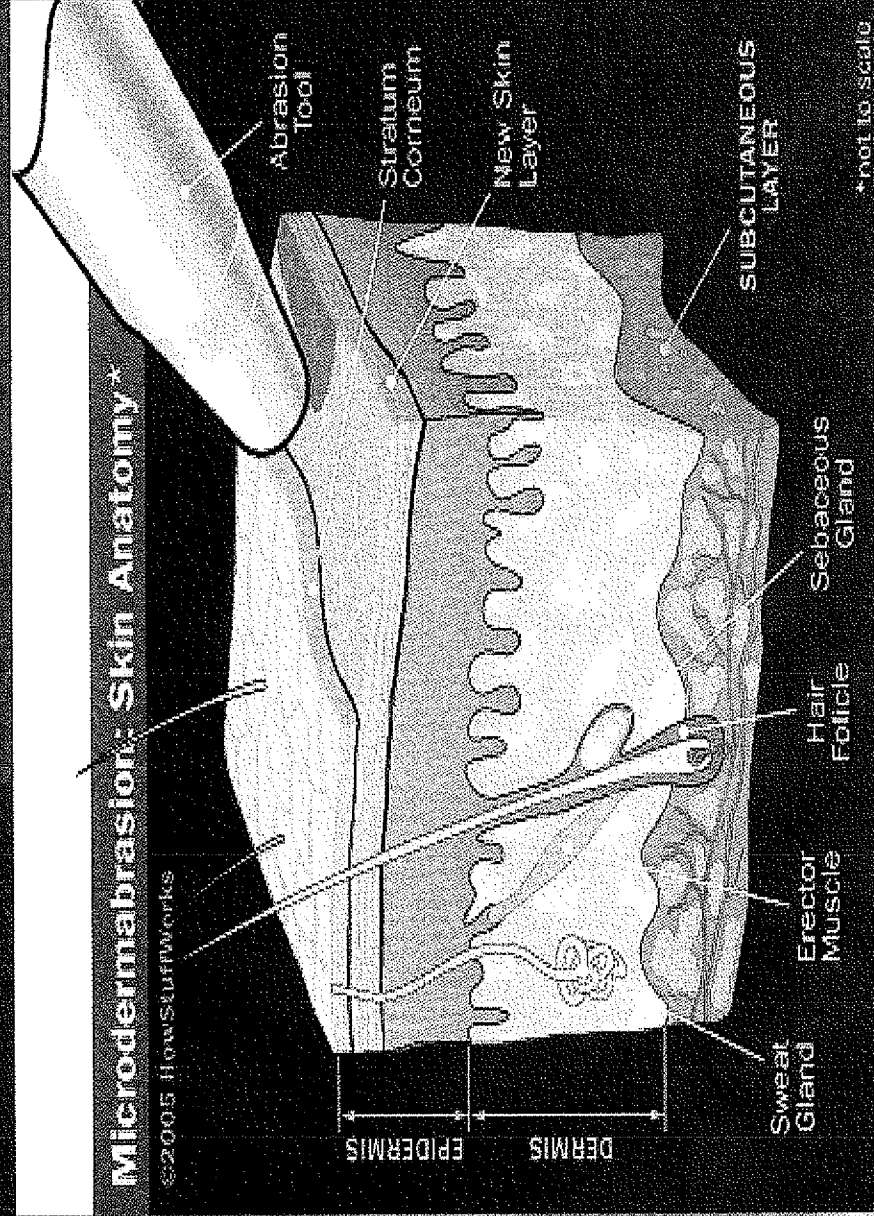
connected pigment cells distribute melanin evenly

supporting skin structure is strong and resilient



FemmePharma
GLAXO BIOPHARM, INC.

Microabrasion Damage to Skin



FemmePharma
A WOMAN'S HEALTHCARE SOLUTION

Comparative Pharmacokinetics of Oral and Mammary Applied Danazol

**Approved oral danazol for FBD 50 to 200
mg twice daily**

Oral 200 mg twice daily

C_{max} ~180 ng/ml

Danazol Gel 80 mg once daily

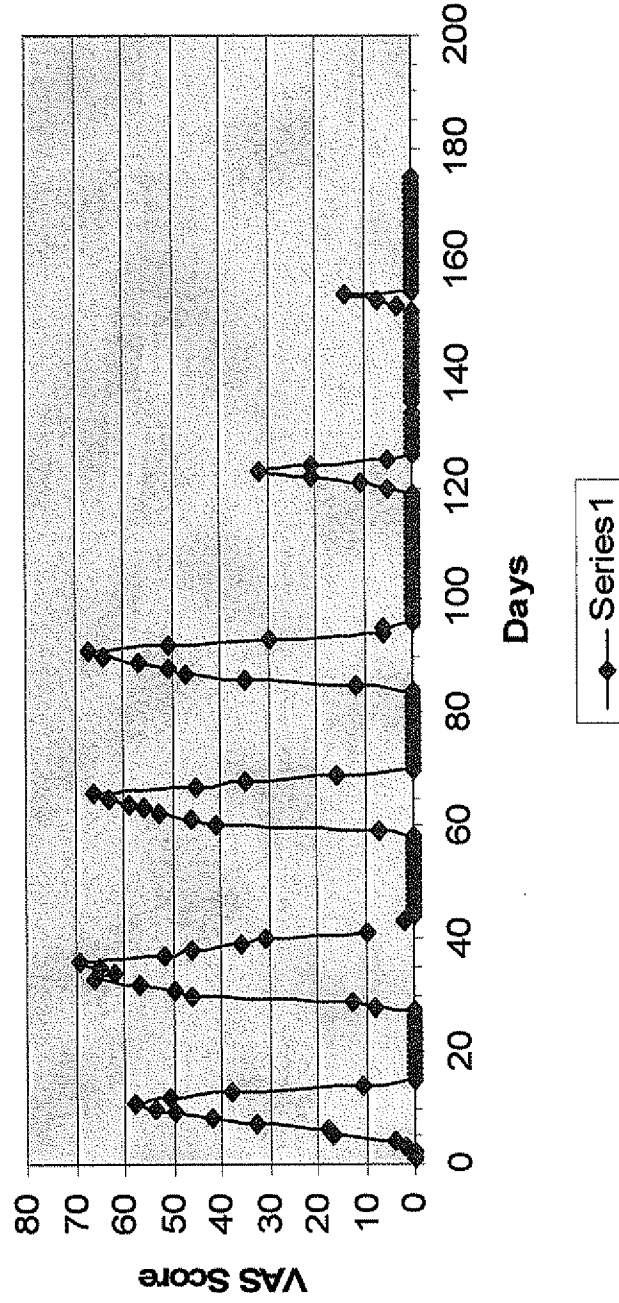
C_{max} <2.75 ng/ml



FemmePharma
A GUYAN PHARMACEUTICAL INC.

Pain Reduction with Danazol Gel in Breast Disease

Subj. 24/072



2/2/2010 Brenda Frazier, Jennifer Kim Family
P.R. AR
GenD. Pianos Peter Mayer, John Zenniah

GD discussed company & its woman-oriented focus

areas of interest: endometriosis

urinary incontinence phase III

fibrocystic breast disease

Phase IIb clinical trial

for pain associated w/ fibrocystic breast disease

danazole administered systemically has significant androgenic side effects

no other treatment

affects 26M women in US

no systemic side effects in clinical trial
still looking at dose

JZ - WO 00/72883

into skin not transdermal

particle are not dissolved into by

doses are different

purpose is different

hydrogel - water + viscosity modifier + crystalline structure
hydroalcoholic - water + alcohol + penetration enhancer

Rec'd for Docketing on:

JAN 10 2010

Docketed by GJG on 2-18-10

Given to ZFB on 2-18-10

②

2/2/2010 12 - danazol is not soluble in water
GD - danazole could be administered

Rapavan - PVP

PM - 2-pyrrolidini

N-methyl-2-pyrrolidin

Comparison to literature
No transdermal penetration to brain

Amendment

In the claims

1. (currently amended) A drug formulation comprising
~~a drug selected from the group consisting of danazol, bromocriptine, and luteinizing hormone-releasing hormone (LHRH) analogues in an amount effective to provide regional~~
providing regionally effective, not systemic systemically effective, levels of danazole when
administered transdermally to the breast, to provide relief from benign diseases or disorders of
the breast,

wherein the danazole is formulated in a hydroalcoholic gel pharmaceutical carrier
~~comprising a transdermal penetration enhancer in which the danazol is soluble to enable promote~~
in an effective amount to deliver
delivery of the drug danazol across the stratum corneum to the breast tissue.

2.-9. (cancelled)

10. (withdrawn, currently amended) A method for treating a disease or disorder of the
treatable with danazol
breast, comprising

topically administering to the breast of a patient,

Same limit
a drug formulation suitable for local or regional delivery comprising an effective amount
of drug selected from the group consisting of danazol, bromocriptine, and luteinizing
hormone-releasing hormone (LHRH) analogues,

in an amount ~~effective to provide regional~~ providing regionally effective, not systemic
systemically effective, levels of danazole when administered transdermally to the breast, to
provide relief from benign diseases or disorders of the breast,

wherein the danazole is formulated in a hydroalcoholic gel pharmaceutical carrier
comprising a transdermal penetration enhancer in which the danazol is soluble to enable promote
delivery of ~~the drug~~ danazol across the stratum corneum to the breast tissue.

11-16. (cancelled)

17. (withdrawn, previously presented) The method of claim 10 wherein the benign
disease of the breast is selected from the group consisting of mastalgia, mastodynia, ~~Mondor's~~,
~~disease~~, fibrocystic breast disease, costochondritis, mastitis, ~~Paget's disease of the areola~~,
~~fibroadenoma, breast abscess, and breast infections~~.

18. (cancelled)

19. (withdrawn, previously presented) The method of claim 10 wherein the region is the
breast, areola, and underlying musculature of the chest.